REMARKS/ARGUMENTS

Claims 16-24 are pending in the application. Claims 22 and 24 have been amended for clarity. No new matter is added by the amendments. Entry of the Amendment and reconsideration of the claims in view of the following Remarks is respectfully requested.

Interview

The Applicants thank the Examiner and his Supervisor for the interview conducted in this case on February 8, 2005, wherein the outstanding rejections of the claims and the teachings of the cited art were discussed.

35 U.S.C. 103

Claims 16-24 were rejected under 35 U.S.C. 135 103(a) as unpatentable over Huland et al. (Huland) in view of both Debs et al. (Debs) and Ruskewicz et al. (Ruskewicz) as further evidenced by Nayar et al. (Nayar) or Hora et al. (Hora). Applicants respectfully traverse this rejection.

Independent claim 22 recites an aerosol composition having a known gamma-IFN biological activity and comprising "a stabilizing agent consisting of sugar, alcohol, amino acid, or combination thereof" and wherein "the composition does not include serum albumin." Independent claim 24 recites an aerosol composition having a known gamma-IFN biological activity and comprising a stabilizing agent that "is a sugar, alcohol, amino acid, or combination thereof" and wherein "the composition does not include serum albumin." Claims 22 and 24 also each recite that the aerosol formed from a gamma-IFN soluion have a "γ-IFN biological activity substantially the same as that of the solution."

Applicants submit that Huland does not teach an aerosol composition having these limitations. Rather, Huland discusses aerosolization of cytokine solutions, and exemplifies aerosolization of IL-2. The solutions to be aerosolized in Huland contain serum protein (preferably human serum albumin) as a stabilizing agent (see column 5, lines 23-27). Huland suggests that other additives can be added to the solution, such as sugar or amino acids (see column 5, lines 45-57); however, the reference nowhere discloses the use of any additives other than serum protein as a stabilizing agent.

It is the Applicants who have discovered that a sugar, alcohol, amino acid, or

combination thereof can stabilize gamma-IFN during aerosolization, maintaining a level of gamma-IFN biological activity substantially the same as that of the gamma-IFN in solution. Applicants submit that Huland nowhere teaches or suggests use of these compounds as stabilizing agents, while maintaining substantially all of the biological activity of gamma-IFN in an aerosol.

The compositions disclosed in Huland are not inherently stabilized by a sugar, alcohol, or amino acid. Huland clearly teaches that compositions comprising a sugar, alcohol, or amino acid display **reduced** biological activity in the absence of serum protein as a stabilizing agent. As discussed in the previous Response and acknowledged by the Examiner, Huland teaches serum protein in the aerosol composition is necessary to optimize the biological effect of the cytokine, and to recover the cytokine after nebulization.

> "The purpose of the serum protein is to optimize the biological effect of the cytokine, and to lead to a better recovery after in vitro nebulization" (column 5, lines 24-27).

Huland discloses that serum protein concentrations of between 0.1-20% by weight of the aerosol correlated in a dose-dependent manner with the level of recovery of the cytokine after nebulization (column 5, lines 35-37). Furthermore, Huland teaches that only at very high levels of cytokine (at least 0.5 mg/ml) can the serum protein be omitted while still allowing recovery and biological activity of the drug (column 5, lines 37-39). Accordingly, Huland explicitly asserts that the level of recovery of cytokine after nebulization correlates in a dose-dependent manner with serum protein concentration. Consequently, the aerosol compositions taught by Huland depend on the presence of serum albumin as an agent to stabilize the cytokine aerosol.

The Examiner's attention is further called to Example 3 of Huland. This Example discloses a composition containing Interleukin-2, dextrose, mannitol, and various concentrations of human serum albumin (HSA). Huland discloses that "[w]ith 0.5% HSA the average recovery of 45 nebulizations was 17%, with 2.0% HSA the average recovery of 45 nebulizations was 28%, with 5% the average recovery was 36%" (column 7, lines 51-54). Huland clearly teaches the necessity of HSA as a stabilizing agent in the composition. Consequently, Applicants submit that none of the compositions disclosed by Huland are inherently stabilized by a sugar, alcohol, amino acid, or combination thereof, as recited by the present claims. Indeed, Huland clearly discloses the contrary, namely, that the presence of these additives did not stabilize cytokine aerosols so that the biological activity of the cytokine was substantially the same as that of the

cytokine in solution.

Furthermore, the present claims recite IFN-gamma compositions. Huland does not teach the stabilization of aerosolized IFN-gamma, but rather only lists IFN-gamma as a cytokine that may be stabilized by HSA. Applicants submit that Huland nowhere teaches or suggests the use of a sugar, alcohol, or amino acid as a stabilizing agent in a composition comprising gamma-IFN.

Applicants further submit that none of the other cited references remedy the foregoing deficiencies. Debs discloses an IFN-gamma aerosol formed from a solution comprising IFN-gamma, buffer, NaCl, and HEPES (paragraph bridging pages 3482-3483). Debs nowhere teaches or suggests the use of a sugar, alcohol, amino acid, or combination thereof to stabilize aerosolized IFN-gamma. Furthermore, Debs discloses aerosolized gamma-IFN having some degree of biological activity, but nowhere teaches or suggest that the aerosolized IFN-gamma has a biological activity that was substantially the same as that of the IFN-gamma in solution, as recited by the present claims.

Ruskewicz is directed to an aerosol extrusion mechanism. This reference nowhere teaches or suggests the use of sugar, alcohol, amino acids, or a combination thereof as stabilizing agents for IFN-gamma aerosols.

Nor do Nayar or Hora teach or suggest an IFN-gamma aerosol composition comprising a stabilizing agent consisting of a sugar, alcohol, amino acid, or combination thereof, and wherein the composition does not include serum albumin.

Hora is directed to compositions comprising IL-2, and additionally comprising a stabilizer such as arginine, carnitine, sugar, or serum albumin (column 2, lines 19-29). This reference nowhere teaches or suggests0 an IFN-gamma solution that does not contain serum albumin, and where activity of the aerosolized IFN-gamma is substantially the same as that of the solution.

Nayar is directed to an albumin-free Recombinant Factor VIII (rFVIII) formulation. This reference nowhere teaches or suggests an IFN-gamma solution that does not contain serum albumin, and where activity of the aerosolized IFN-gamma is substantially the same as that of the solution.

Applicants submit that one of skill in the art would not reasonably predict that the disclosed serum protein-free compositions of Hora or Nayar for stabilizing IL-2 or Factor VIII

would also stabilize IFN-gamma aerosols. Indeed, Nayar teaches away from such a prediction. Nayar discloses a formulation for Factor IX that "appears similar to the formulation for rFVIII disclosed herein" (column 2, lines 27-29). Nayar asserts, however, that

> "[I]t is well known that Factor VIII is inherently more unstable than FIX and freeze dried concentrates of each factor demonstrate marked differences in stability on storage at various temperatures. Unlike FVIII, FIX includes unique gamma carboxylation of 12N terminal glutamic acid residues, thus providing a possible basis for differential stability. Thus a formulation for FIX would not necessarily suggest a formulation for FVIII" (column 2, lines 38-45).

Therefore, Nayar teaches away from the notion that serum-free compositions disclosed would stabilize proteins other than FVIII, such as IFN-gamma. Indeed, and as discussed in the previous Response and accompanying Declaration, IFN-gamma possesses unique features that were known to adversely affect its stability upon aerosolization. Specifically, it was known that IFN-gamma is active in a non-covalent dimeric form, but not in monomeric form, and that it is believed that aerosolization may lead to loss of activity by creating shear conditions that result in the conversion of IFN-gamma to inactive monomeric forms. Consequently, serum-free compositions containing the stabilizers disclosed in Nayar or Hora could not be reasonably predicted to stabilize IFN-gamma.

Applicants submit with this Response a paper directed to the stabilization of aerosolized gamma-IFN using liposomes (Kanaoka et al.) Kanaoka teaches that gamma-IFN is unstable in nebulization (Abstract and first full paragraph), that gamma-IFN "is known to be inactivated by mechanical stress," and that "mechanical stress is very strong in nebulization" (page 170, second full paragraph). Kanaoka concludes that "[i]t must be very easy to aggregate IFN-γ by such a strongly mechanical shearing." *Id.*

Kanaoka discloses stabilizing aerosolized gamma-IFN through the addition of small liposomes. Kanaoka found that the use of liposomes as a stabilizing agent resulted in a gamma-IFN recovery of about 25% to 27% upon nebulization (page 168, first paragraph). The use of a control gamma-IFN solution without liposomes, however, resulted in recovery of only 0.4% to 3.1%. *Id.*

Due to the unique instabilities associated with IFN-γ, success in stabilizing aerosolized IFN-gamma could not be reasonably predicted by the teaching of Nayar or Hora.

Furthermore, neither Nayer nor Hora disclose use of stabilizing agents to stabilize cytokines aerosols. Both Nayer and Hora are directed to the use of stabilizing agents to stabilize protein compositions in lyophilized forms. Neither reference discusses or suggests the stabilization of aerosolized cytokines. Therefore, one would not look to Nayer or Hora for methods of stabilizing IFN-gamma aerosols.

Applicants submit that claims 16-24 are patentable over the cited references, alone or in any combination, for at least the foregoing reasons. Withdrawal of the rejection is therefore requested.

Claims 16-24 were rejected under 35 U.S.C. 103(a) as unpatentable over Huland and Jaffe in view of both Debs and Ruskewicz, as further evidenced by Nayar or Hora. Applicants traverse this rejection for the same reasons discussed above. Namely, Huland neither teaches nor suggests the IFN-gamma compositions as claimed, comprising a stabilizing agent consisting of a sugar, alcohol, or amino acid, where the composition does not include serum albumin, and where the aqueous droplets posses a IFN-gamma biological activity substantially the same as that of the solution. Furthermore, none of the remaining references, alone or in any combination, remedy this deficiency.

The disclosures of Debs, Ruskewicz, Nayar , and Hora have been discussed above. Jaffe discloses IFN-gamma formulated in an excipient composed of sodium succinate, mannitol, and polysorbate 20. Aerosolization is not disclosed. The Examiner concludes that this formulation stabilizes the rIFN-gamma, as evidenced by Nayar and Hora , without including serum albumin in the composition. Applicants disagree.

Applicants submit that neither Nayar nor Hora are relevant in establishing the activity of the rIFN-gamma aerosol taught by Jaffe. As discussed above, neither of these references are directed to gamma-IFN. Indeed, as discussed above, Nayer teaches away from the use of the disclosed stabilizing agents to stabilize other cytokines. Furthermore, neither of these references is directed to cytokine aerosols. Nayer and Hora are directed to the stabilization of lyophilized protein compositions. Consequently, one would not look to Nayer or Hora for methods of stabilizing IFN-gamma aerosols.

Applicants submit that claims 16-24 are patentable over Huland and Jaffe in view of both Debs and Ruskewicz, as further evidenced by Nayar or Hora, for at least the foregoing reasons. Withdrawal of the rejection is therefore requested.

35 U.S.C. 112, first paragraph

Claims 15, 22, and 24 were rejected under 35 U.S.C. 112, first paragraph as failing to comply with the written description requirement. The Examiner contends that Applicants have not "explicitly recited in the specification or the originally filed claims that the composition does not include serum albumin." Applicants disagree.

As an initial matter, the Examiner is reminded that the specification need not explicitly recite support for the literal language of the claims. Rather, claims can be supported by the specification "through express, implicit, or inherent disclosure." *MPEP 2163 I. B.*

Applicants submit that the specification clearly supports claims to aerosol compositions that do not include serum albumin. In Table 1, the specification specifically discloses an IFN-gamma solution that does not comprise serum albumin. As stated in the previous Response, the use of serum protein as a stabilizing agent was known in the prior art, as evidenced by Huland. Applicants have specifically exemplified an IFN-gamma solution that does not contain serum protein. Therefore, the skilled artisan would readily apprehend that Applicants were in possession of IFN-gamma compositions that do not include serum protein at the time of filing of the present application.

Applicants submit that the claims are fully supported by the specification, for at least the foregoing reasons. Withdrawal of the rejection is therefore requested.

The Examiner also contends that while the specification discloses stabilizing agents such as sugar, alcohol, and amino acids, it does not describe the combination of these agents. Applicants disagree with this rejection.

The test for sufficiency of support in an application is whether the disclosure at the time of filing "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." MPEP 2163.02 (quoting *In re Kaslow*, 707 F.2d 1366, 1375 (Fed. Cir. 1983). The description as filed is presumed to be adequate, unless or until sufficient evidence or reasoning to the contrary has been presented by the examiner to rebut the presumption." MPEP 2163 III. A. It is the Examiner who bears "the initial burden of presenting by a preponderance of evidence why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims." MPEP 2163. III. A. Furthermore, the Examiner is reminded that "[m]ere rephrasing of a passage does not constitute new matter." MPEP 2163.07 I.

Applicants submit that in light of the foregoing guidelines, the disclosure clearly conveys to the artisan that Applicants were in full possession of the subject matter of claim 24. Claim 15 originally recited an aqueous IFN-gamma solution "containing a stabilizing agent." The term "containing" is an open-ended term that is comparable to the term "comprising." MPEP 2163 II. A. 1. The disclosure specifically recites that each of sugar, alcohol, or amino acid are suitable for use as stabilizing agents in the present invention (page 7, lines 26-28). Applicants submit the original claim language clearly includes within its scope an aqueous gamma-IFN solution comprising a combination of sugar, alcohol, or amino acid as stabilizing agents.

Claim 15 as amended recites aqueous gamma-IFN solution "comprising a stabilizing agent consisting of sugar, alcohol, amino acid, or a combination thereof." Applicants respectfully submit that the phrase "a combination thereof" is merely a rephrasing of the original claim language of original claim 15, which also included within its scope a combination of stabilizing agents. The phrase "a combination thereof" does not alter the meaning of the claim, and is therefore proper as is indicated by the MPEP.

Furthermore, as stated above, the disclosure specifically recites that each of sugar, alcohol, or amino acid are suitable for use as stabilizing agents in the present invention. Given this disclosure, it would reasonably be expected that a combination of these compounds would also be effective as a stabilizing agent. Consequently, on reading the specification it is readily understood that Applicants were in possession of aerosol compositions comprising a stabilizing agent that is a combination of sugar, alcohol, or amino acid at the time of the invention. Applicants submit that the Examiner has not articulated any reason why the disclosure that sugars, amino acids, and alcohols are suitable stabilizing agents would not immediately and reasonably convey that a combination of these agents would also be suitable, and that Applicants therefore were in possession of this embodiment. Therefore, the Examiner has not met the initial burden of demonstrating a lack of written support. Applicants submit that the specification provides ample support for new claim 24 as written, at least for the foregoing reasons. Withdrawal of the rejection is therefore respectfully requested.

Summary

Applicants submit that the claims are in condition for allowance, and notification to that effect is earnestly solicited. The Examiner is invited to contact Applicants' representative if prosecution may be assisted thereby.

Respectfully submitted,

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